

REMARKS

Claims 1-3, 7-15, 20-24, 28 and 30 are pending. Claims 19 and 29 have been canceled. Claims 4-6, 8-12, 15-18 and 25-27 have been withdrawn. Claims 23 and 24 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Support for the amendment to claims 23 and 24 can be found, for example, in original claims 23 and 24, respectively. No new matter has been added.

I. REJECTION OF CLAIMS 1-3, 7, 13, 14, 20-24 AND 28 AND 30 UNDER 35 U.S.C. § 103(a)

Claim 1-3, 7, 13, 14, 20-24, and 28-30 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over United States Patent No. 5,998,457 to Kaddurah-Daouk (“Kaddurah-Daouk”) in view of United States Patent No. 4,772,591 to Meisner (“Meisner”), United States Patent No. 5,888,553 to Grant *et al.* (“Grant”), United States Patent No. 5,756,496 to Beale *et al.* (“Beale ‘496”) and United States Patent No. 5,716,926 to Beale *et al.* (“Beale ‘926”). The Office Action alleges that “Kaddurah-Daouk teaches a method of treating osteoporosis or osteoarthritis comprising administering therapeutic [sic] effective amount of creatine compound, or a pharmaceutical [sic] acceptable salt, to patient” (Office Action, page 2, ¶ 4, lines 18-20). The Office Action further alleges that “Grant *et al.* teaches that the excess of cortisol is known to be a cause of osteoporosis, tissue degeneration, and an anabolic composition with anticortisol effect are used to balance the effect of cortisol. The anabolic composition comprising creatine” (Office Action, page 3, ¶ 6, lines 3-5). The Office Action still further alleges that “Beale (‘469) teaches creatine pyruvate (pyruvyl-creatine) is particularly useful as cortisol antagonist or cortisol blocker for prevent [sic] the catabolic activity of cortisol ... [and], Beale (‘926) further teaches that pyruvate is known to be useful for treating osteoporosis” (Office Action, page 3, ¶ 8, lines 10-13). The Office Action contends that “a person of ordinary skill in the art would have been motivated to employ creatine pyruvate for treating connective tissue degenerative disorders, including those unrelated to weight gain or lose [sic], such as osteoporosis, osteoarthritis or periodontitis, or for accelerating wound healing, promoting growth of connective tissue (cartilage) because it is *prima facie* obvious to combine two or more compounds each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very [sic] same purpose; the idea of combining them flows logically from their having been individually taught in the prior art” (Office Action, page 3, ¶ 6, line 20 - page 4, line 5).

The Office Action concludes: “[T]hus, the claimed invention which employs a combination (salt) of two compounds known to be useful for treating osteoporosis sets forth the prima facie subject matter” (Office Action, page 4, ¶ 6, lines 5-7).

Applicants respectfully traverse.

A. Claims 1-3, 7, 13,14 and 20-22 are not Obvious over Kaddurah-Daouk in view of Grant, Meisner, Beale ‘496 and Beale ‘926’

Claims 1-3, 7, 13, 14 and 20-21 are directed to a method of treating a bone or cartilage condition comprising administering to an animal a therapeutically effective amount of an agent comprising creatine, or an analogue or pharmaceutically acceptable salt thereof, to treat bone or cartilage conditions; and claim 22 is directed to a method of promoting growth and mineralization of bone or cartilage cells and tissues comprising administering to a subject a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof. Claims 1-3, 7, 13, 14 and 20-22 further require that the agent comprising creatine is essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine. As Applicants noted in the Amendment filed on June 25, 2003, no combination of the cited references discloses, suggests, or teaches a method comprising administration of a composition essentially free of one or more of dihydrotriazine; dicyano-diamide; or creatinine, as set forth in claims 1 and 22.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974).

The combination of Kaddurah-Daouk, Grant, Meisner, Beale ‘496 and Beale ‘926 does not disclose, teach or suggest a method of using an agent comprising creatine **that is essentially free** of one or more of dihydrotriazine; dicyano-diamide; or creatinine as required by claims 1-3, 7, 13, 14 and 20-22 of the present invention. And because the combination of Kaddurah-Daouk, Grant, Meisner, Beale ‘496 and Beale ‘926 does not teach or suggest all the claim limitations of claims 1-3, 7, 13, 14 and 20-22, the claims are not prima facie obvious over the cited references.

Additionally, Applicants submit that Grant is directed to the use of chromium to decrease cortisol levels and expressly teaches that “[i]t is also **necessary** that adequate amounts of chromium and magnesium, in a bioavailable form, are present to regulate enzyme functions, cortisol levels, and optimize synthesis of proteins, glucose, and fat distribution” (Grant, col. 4, lines 63-67) (emphasis added).

Thus, even if the method taught by the combination of Kaddurah-Daouk, Grant, Beale '496, Meisner and Beale '926 could be used to treat a subject as claimed in claims 1-3, 7, 13, 14 and 20-22, the method taught by that combination of references would require an agent comprising a chromium compound in view of the express teachings of Grant.

The omission of an element and retention of its function is an indicia of unobviousness. *In re Edge*, 359 F.2d 896 (CCPA 1066).

Because the method of claims 1-3, 7, 13, 14 and 20-22 omits a chromium compound, the method of claims 1-3, 7, 13, 14 and 20-22 would be unobvious over a method of treating a subject with a composition requiring chromium as taught by Grant in combination with Kaddurah-Daouk, Beale '496, Meisner and Beale '926. Therefore, claims 1-3, 7, 13, 14 and 20-22, which do not recite a chromium compound, are not obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926.

Thus, in view of the above, Applicants respectfully request that the rejection of claims 1-3, 7, 13, 14 and 20-22 under 35 U.S.C. § 103(a) as allegedly obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926 be withdrawn.

B. Claims 22-24, 28 and 30 are not Obvious Over Kaddurah-Daouk in view of Grant, Meisner, Beale '496 and Beale '926

Claims 22-24, 28 and 30 are directed to various methods of treating a subject with an agent comprising creatine or an analogue thereof, a pharmaceutically acceptable salt of creatine or analog thereof, creatine kinase and/or creatine pyruvate. Claim 22 is directed to a method of promoting growth and mineralization of bone or cartilage cells and tissues and requires administering to a subject a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof; claim 23 is directed to a method of improving acceptance and osseous integration of bone implants comprising administering to a subject in need of such treatment a therapeutically effective amount of an agent comprising creatine or an analogue thereof or a pharmaceutically acceptable salt of creatine or analog thereof, to improve acceptance and osseous integration of bone implants; and claim 24 is directed to a method for accelerating healing in a subject having a defect in bone or cartilage tissue caused by trauma or surgery comprising administering to the subject a therapeutically effective amount of at least one of (1) a creatine compound or analogue thereof, (2) a pharmaceutically acceptable salt of creatine or analog thereof, and (3) a creatine kinase. The Office Action

alleges that “[c]laims 22-24 are obvious because creatine is known to be useful for promoting tissue repair process, and treating osteoarthritis and osteoporosis would also be considered as a process of promoting tissue (cartilage) repairing since one of the major symptoms of osteoarthritis and osteoporosis is tissue degeneration” (Office Action, page 4, ¶ 6, lines 11-14).

Claim 28 is directed to a method of treating osteoarthritis unrelated to weight gain or weight loss comprising administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof; and claim 30 is directed to a method of treating at least one bone or cartilage condition comprising administering to an animal a therapeutically effective amount of an agent comprising creatine pyruvate or an analogue thereof. The Office Action alleges: “As to claims 28 and 30, note, in view of the teachings of Beale, Meisner and Grant, one of ordinary skill in the art would have appreciated that therapeutic effect of creatine pyruvate is not limited only to symptoms related to weight gain or weight loss” (Office Action, page 4, ¶ 6, lines 14-17)

Applicants respectfully traverse.

Kaddurah-Daouk is directed to “a method of treating or preventing a metabolic disorder which relates to an imbalance in the regulation of body weight” (Kaddurah-Daouk, col. 2, lines 44-46). Kaddurah-Daouk describes a number of metabolic disorders including “obesity and its related disorders (such as cardiovascular disease, hypertension, diabetes, hyperlipidaemia, osteoporosis and osteoarthritis) and severe weight loss” (Kaddurah-Daouk, col. 2, lines 46-49). The method of Kaddurah-Daouk “consists of administering to a patient susceptible to or experiencing said disorder a creatine compound (creatine analogues and compounds which modulate one or more of the structural or functional components of the creatine kinase/creatine phosphate system)” (Kaddurah-Daouk, col. 2, lines 49-54). The Office Action concedes that “Kaddurah-Daouk does not teach expressly the employment of creatine pyruvate for the treatment, or the particular amount administered, or the method may be employed for promoting growth and mineralization of bone; improving acceptance and osseous integration of bone; or accelerating healing as claimed in claims 22-24” (Office Action, page 2, ¶ 5, line 21 - page 3, line 2). Applicants submit that these deficiencies of Kaddurah-Daouk are not overcome further in view of Grant, Meisner, Beale ‘496 and Beale ‘926.

The Office Action alleges that “Grant et al. teaches that the excess of cortisol is known to be a cause of osteoporosis, tissue degeneration, and an anabolic composition with anticortisol effect are used to balance the effect of cortisol. The anabolic composition

comprising creatine” (Office Action, page 3, ¶ 6, lines 3-5). However, Applicants submit that Grant teaches the use of chromium to decrease cortisol levels. Grant states: “Supplemental chromium, administered to bovine species, has been shown to decrease serum cortisol and may increase milk production. Supplemental chromium has also has been found to be associated with weight gain in stressed animals. Part of the improvement in gain with administering supplemental chromium may be due to decreasing cortisol production” (Grant, col. 3, lines 25-30). Grant further teaches that “[i]t is also necessary that adequate amounts of chromium and magnesium, in a bioavailable form, are present to regulate enzyme functions, cortisol levels, and optimize synthesis of proteins, glucose, and fat distribution” (Grant, col. 4, lines 63-67).

Beale ‘469 “relates to a composition which comprises pyruvate and/or derivatives of pyruvate and an anti-cortisol or cortisol blocker compound” (Beale ‘469 , col. 2, lines 11-13). Beale teaches: “Creatine monohydrate is an additional cortisol blocker that, when combined with pyruvate, produces a synergistic effect in increasing the lean body mass of a mammal. The combination of pyruvate and creatine monohydrate also produces an increase in the athletic performance of the mammal by enhancing the energy level of the mammal” (Beale ‘469, col. 3, lines 58-63). The Office Action states that “Beale (‘469) teaches creatine pyruvate (pyruvyl-creating) is particularly useful as cortisol antagonist or cortisol blocker for prevent [sic] the catabolic activity of cortisol” (Office Action, page 3, ¶ 8, lines 10-12).

The Office Action alleges that “Meisner teaches a method for accelerated wound healing or treating degenerative disorders including periodontal disease, [or] osteoarthritis, comprising administering a composition comprising creatine to an animal or human” (Office Action, page 3, ¶ 6, lines 6-9). Meisner is directed to a method which “comprises the administration of four substances: a source of biologically available calcium; ascorbic acid; a precursor or stimulant of epinephrine or nor-epinephrine production selected from tyrosine and phenylalanine; and a mild anti-inflammatory substance selected from the anti-inflammatory members of the group consisting of simple sugars, amino sugars, amino acids, and derivatives thereof” (Meisner, col. 2, line 67 - col. 3, line 6). Meisner describes a number of anti-inflammatory substances, one being creatine (Meisner, col. 5, lines 10-19). However, Meisner does not exemplify creatine, nor does Meisner disclose or teach or suggest that creatine is preferable to the other anti-inflammatory substance.

The Office Action further alleges that “Beale (‘926) further teaches that pyruvate is known to be useful for treating osteoporosis” (Office Action, page 3, ¶ 8, line 13).

Beale '926 is directed to a method which "comprises administering to a mammal in need of enhancing its protein concentration or muscle mass, a composition comprising pyruvate and a source of amino nitrogen having specific types and levels of amino acids" (col. 1, lines 15-19). However, Beale '926 does not disclose, teach or suggest any creatine compound or analogue thereof such as, for example, creatine pyruvate.

In summary, Kaddurah-Daouk teaches a method of treating metabolic disorders but does not teach the use of creatine pyruvate for promoting growth and mineralization of bone, improving acceptance and osseous integration of bone, or accelerating healing. Applicants further note that Kaddurah-Daouk does not disclose teach or suggest a method of treating a disorder related to excess cortisol. In contrast, Grant expressly teaches regulating cortisol levels and expressly teaches the use of a chromium-containing compound; Beale '496 teaches that creatine pyruvate (pyruvyl-creatine) is particularly useful as a cortisol antagonist or cortisol blocker for preventing the catabolic activity of cortisol; Meisner teaches a method for treating wound healing comprising the administration of four substances including a mild anti-inflammatory substance, but does not exemplify a creatine agent as a mild anti-inflammatory substance or teach that a creatine agent is preferred; and Beale '926 does not disclose, teach or suggest any creatine compound.

To make out a prima facie case of obviousness the references cited to reject the claims must provide all of the elements of the invention as claimed and a suggestion must be found within the references themselves to combine the disclosures of the various cited art references to make the claimed invention. *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery*, 804 F.2d 135, 140 (Fed. Cir. 1986); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577 (Fed. Cir. 1984).

Applicants submit that one skilled in the art would find no suggestion to combine Grant and Beale '496 (which are directed to regulating cortisol) with Kaddurah-Daouk, which does not disclose, teach or suggest cortisol. Applicants further submit that the lack of suggestion to combine Grant and Beale '496 with Kaddurah-Daouk is not overcome further in view of Meisner (which does not state a particular reason to choose creatine) and Beale '926 (which does not disclose, teach or suggest any creatine compound). Because one skilled in the art would find no suggestion to combine Kaddurah-Daouk, Grant, Beale '496, Meisner and Beale '926 and thereby arrive at the presently claimed invention, claims 22-24,

28 and 30 are not obvious over the combination Kaddurah-Daouk, Grant, Beale '496, Meisner and Beale '926.

Also as noted above, even if the method taught by Kaddurah-Daouk, Grant, Beale '496, Meisner and Beale '926 could be used in a method for treating a subject as claimed in claims 22-24, 28 and 30, that method taught by the combination of references would require an agent comprising a chromium compound in view of the express teachings of Grant.

The omission of an element and retention of its function is an indicia of unobviousness. *In re Edge*, 359 F.2d 896 (CCPA 1066).

Because the method of claims 22-24, 28 and 30 omits a chromium compound, the method of claims 22-24, 28 and 30 would be unobvious over a method of treating a subject with a composition requiring chromium as taught by Grant in combination with Kaddurah-Daouk, Beale '496, Meisner and Beale '926. Therefore, claims 22-24, 28 and 30, which do not recite a chromium compound, are not obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926.

Thus, for the reasons provided above, the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926 does not disclose, teach or suggest a method of treating a subject with an agent comprising creatine or an analogue thereof; a pharmaceutically acceptable salt of creatine or analog thereof; creatine kinase and/or creatine pyruvate as required in claims 22-24, 28 and 30 of the present invention. Therefore, Applicants respectfully request that the rejection of claims 22-24, 28 and 30 under 35 U.S.C. § 103(a) as allegedly obvious over the combination of Kaddurah-Daouk, Grant, Meisner, Beale '469 and Beale '926 be withdrawn.

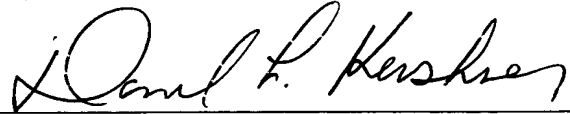
II. CONCLUSION

Applicants respectfully submit that the present claims are now in condition for allowance and request an early issuance of a Notice of Allowance in connection with the present application.

If the Examiner wishes to discuss this case, then Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and expedite the allowance of the application.

Date: March 23, 2004

Respectfully submitted,



By: David L. Kershner

Reg. No. 53,112

For: Brian Rothery

Reg. No. 35,340

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939